This Page Is Inserted by IFW Operations
and is not a part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

(12) UK Patent Application (19) GB (11) 2 229 443 (13) A

(43) Date of A publication 26.09.1990

(21) Application No 8905138.7

(22) Date of filing 07.03.1989

(71) Applicant
American Cyanamid Company

(Incorporated in the USA - Maine)

Berdan Avenue, Township of Wayne,
New Jersey 06904, United States of America

(72) Inventors
Mark Gibson
Nicholas Ian Payne
Philip Leon Gould
Peter Mark Taylor

(74) Agent and/or Address for Service
Lloyd Wise Tregear & Co
Norman House, 105-109 Strand, London, WC2R 0AE,
United Kingdom

(51) INT CL[5]
C08L 71/02, A61L 15/16, C08L 1/08

(52) UK CL (Edition K)
C3M MXX M112 M112A M122 M162 M200
A5R RBF
U1S S1049 S3001 S3012 S3016 S3069

(56) Documents cited

GB 2200643 A	GB 2064556 A	GB 2048292 A
GB 2042572 A	GB 2036042 A	GB 2021125 A
GB 1594389 A	GB 1522087 A	EP 0075791 A
US 4036808 A	US 3758641 A	

(58) Field of search
UK CL (Edition J) A5R, C3L, C3M, C3V
INT CL[4] A61L

(54) Wound dressings

(57) A wound dressing composition comprises a gel-forming component and a film-forming component in amounts such that the composition is a pourable fluid at the time of application and then in contact with the skin forms a non-flowable gelatinous wound dressing whose characteristic can range from a rigid gel to a flexible, coherent film, depending on the relative proportions of the gel-forming and film-forming components.

GB 2 229 443 A

IMPROVED WOUND DRESSING

This invention relates to a novel type of wound dressing which can be adapted for application to both superficial and deep-seated wounds.

In recent years the traditional woven and non-woven sheet-form wound dressings have been supplemented by a variety of newer types of wound dressing. Amongst these recently introduced wound dressings are so-called film dressings and gel dressings.

Film dressings consist of a transparent, semi-permeable film of polyurethane or other synthetic polymer, often coated on one side with an adhesive by which the dressing can be adhered to the wound site. They are now widely used, in the treatment of superficial wounds and burns, their permeability to air and water vapour allowing the tissue to remain in an environment conducive to optimum wound healing. However, film dressings do not absorb excess exudate and toxic components from the wound, which means that generally they are unsuitable for treating deep cavity wounds. Moreover, film dressings can be difficult to apply to certain areas, for example around fingers, toes and joints. Furthermore, they may allow infections to develop underneath the film as a result of tracking of bacteria along ridges and folds in the dressing if good adhesion to the wound has not been achieved.

Gel dressings are available either as self-supporting sheet-like products, as gels or in a non-gelled form capable of forming a gel <u>in situ</u> at the wound site. Unlike film dressings, gel dressings are useful for the treatment of cavity wounds. They provide a material which may expand or otherwise fill the wound cavity and once applied they provide a moist interface to potentiate wound healing. Moreover, gel dressings are often capable of absorbing excess exudate. However the

presently available gel dressings all have the disadvantage of lacking mechanical strength, and consequently, and in contrast to film dressings, they usually require an additional dressing to hold them in place. Further, these gel dressings can be difficult to apply, and in some instances they leave residues which become implanted in new tissue growth.

The currently available film and gel wound dressings have been described in more detail in the literature, see for example Lawrence in "Pharmacy Update", April 1987, pages 147-150; and Turner in "Pharmacy International", June 1985, 131-134.

The object of the present invention is to provide a new wound dressing which has both film- and gel-forming properties, whereby the wound dressing has a combination of advantageous properties not possessed by the existing film and gel dressings.

In accordance with the present invention there is provided a wound dressing composition comprising an aqueous vehicle containing (a) from 1% to 30% by weight of one or more compounds having reversible thermosetting gel properties, and (b) from 5% to 20% by weight of one or more compounds, compatible with component (a) having film-forming properties, said percentages being based on the total weight of components (a) and (b) and aqueous vehicle in the composition, and the composition having a sol-gel transition temperature within the range 10° to 30°C, a viscosity of not greater than 250 poise, as determined by a Brookfield viscometer, at a temperature immediately below its sol-gel transition temperature whereby the mixture is pourable onto a wound to be treated when below said transition temperature, and in contact with the skin setting to form a non-flowable gelatinous wound dressing.

The wound dressing compositions in accordance with this invention are semi-viscous pourable fluids at

relatively low temperatures. They may therefore be applied, from a suitable container, which preferably will have been kept refrigerated (about 3°-8°C) at least immediately prior to use, by being poured onto the open wound, to take up the contours of the wound. To ensure satisfactory pourability at the time of use it is preferred that the viscosity of the aqueous mixture should be from 50 to 250 poise (Brookfield viscometer) immediately below its sol-gel transition temperature. Further, it is preferred that the sol-gel transition temperature should lie between 10°-25°C, more preferably 16°-20°C. With a transition temperature lower than 10°C, then there is a risk that the composition will set too quickly after removal from the refrigerator thus making it difficult, if not impossible, to apply to a wound. Conversely, with a transition temperature above 25°C, the composition can take an undesirable time to set post-application, or in some circumstances may not set at all.

After being applied to the wound site, the composition forms what we term a "gelatinous-film" or "gel-film" as its temperature is raised to ~20°-25°C in contact with the patient's skin, and this gel-film, unlike currently available gel dressings, does not normally require an additional dressing to hold it in place, although, of course, such an additional dressing may be applied if considered expedient by the physician. The characteristics of this gel-film vary somewhat, depending on the quantities of the gel-forming and film-forming ingredients, and on the possible presence of other ingredients. Indeed, it is a particular advantage of this invention that by varying the amounts of the ingredients a range of different wound dressings can be provided to more clearly suit the requirements of different types of wounds.

More particularly, the amounts of the gel-forming and film-forming ingredients can be varied so as to emphasise the film-forming properties or alternatively the gel-forming properties of the compositions.

Thus, it is possible, for instance, to formulate the wound composition so that, on setting, it forms a tough, flexible, coherent film on the skin surface which provides a barrier to microorganisms and good resistance to mechanical stresses. Such a formulation will be particularly suitable for treating superficial wounds such as dermabrasions, skin-graft donor sites, shallow burns, etc. More particularly, compositions which set to form such flexible films can be formed from mixtures comprising from 1% to 5%, preferably 2% to 3%, by weight of the gel-forming component (a) and from 5% to 20%, preferably 8% to 12%, of the film-forming component (b), these percentages again being based on the total weight of components (a), (b) and the water in the composition.

In such compositions, the gel-forming component (a), although present in relatively low concentrations, nonetheless serves to increase significantly the rate of formation of the gelatinous-film so that it sets in a reasonably short time, without impairing the strength or toughness of the set film.

By means of the present invention, and in preferred instances, it is possible to provide wound dressing compositions which set on the skin to form films which:

(1) are strong and durable, yet conformable and elastic, to isolate the wound and provide a barrier to microbial invasion and mechanical stresses;

(2) allow gaseous exchange and water vapour out, but retain sufficient water to maintain a high humidity at the wound dressing interface;

(3) can be readily washed away so that they can be removed without trauma to the patient; and

(4) are clear, colourless and transparent, allowing visual observation and hence control, of the wound through the dressing itself.

In addition, of course, these compositions, indeed like all the compositions of this invention, must be non-antigenic and non-toxic, be sterilizable and be stable on storage.

An alternative approach, emphasising the gel-former rather than the film-former, provides a composition which sets to a rigid gel, and is particularly suitable for the treatment of deep-seated wounds such as leg ulcers and deep burns. By the term "rigid gel" we mean a gel which has a viscosity of at least 8000 poise (Brookfield viscometer) at 25°C. A gel of this viscosity is non-flowable; for instance, the meniscus of the product will not move when it is tilted through 90°. It typically has the consistency of a firm "jelly" such as that produced when gelatin in water is allowed to set, but mechanically stronger. More particularly, compositions which set to form such a rigid gelatinous mass can be formed from mixtures comprising from 5% to 30% by weight, preferably 7% to 20%, of the gel-forming component (a) and from 5% to 15%, preferably 7% to 12%, by weight of the film-forming component (b) these percentages being based on the total weight of components (a), (b) and water present in the compositions.

In these compositions, the film-forming component (b) enhances the rate of gelation of the composition, controls its sol-gel transition and, in some instances can actually increase the gel strength at skin temperatures.

By means of the present invention, and in preferred instances, it is possible to provide wound

dressing compositions which set in contact with a deep-seated wound to form rigid gels which:

(1) readily conform to the wound contours and fill the wound cavity;

(2) are gas and water-vapour permeable whilst providing a barrier to microorganisms and mechanical stresses;

(3) have the ability to absorb excess exudate and toxic substances at the wound site;

(4) have the ability to insulate the wound from body temperature loss;

(5) are easily washed away so that they can be removed without trauma to the patient;

(6) are clear, colourless and transparent, allowing visual observation, and hence control, of the wound through the dressing itself; and

(7) allow aspiration of exudate through the dressing, e.g. by means of a syringe, the access site through the dressing then resealing itself.

In addition, there are the same requirements that the formulations should be non-toxic and non-antigenic, stable on storage and sterilizable.

Of course, it will be understood that the wound dressing compositions of this invention may be formulated so as to have properties intermediate between those of the two types of formulation just referred to.

The concentrations of the components of the composition, as well as the presence of optional ingredients will also affect its gel-setting time to some extent, but this property is also governed by other factors as well, for instance the bulk quantity of product which is applied to the wound will affect the heat transfer into the gel and hence the gel setting time, whilst the temperature at which the composition is dispensed is also important in determining the gel

setting time. Desirably, the gel setting time will be from about 5 to 15 minutes.

A wide range of compounds may be used to provide the gel-forming and film-forming ingredients, respectively, of our compositions.

As is known to those skilled in the art, a number of compounds are available which exhibit reversible gelation properties. Such gel-forming materials are generally block copolymers of polyoxyethylene-polyoxypropylene, for instance those available under the trade name "Pluronic"; or tetrasubstituted derivatives of ethylene diamine where the substituents are block copolymers of polyoxyethylene-polyoxypropylene, for instance those available under the trade name "Tetronic" (see, for example, GB-A-1571832 and EP-A-0126684). It is preferred that the gel-former should exhibit reversible gelation properties at or around skin temperatures, i.e. within the range from 10°-45°C. We have found that "Pluronic" F127 is particularly suitable for the purposes of providing the gel-former in the compositions of this invention, since it is a highly efficient gellant, i.e. it will form a rigid gel at low concentrations, and has an extremely low order of toxicity without adverse effects on the mucous membrane. "Pluronic" 127 is a polyoxyethylene-polyoxypropylene block copolymer of average molecular weight about 11,500.

A mixture of two or more different gel formers may be used if desired.

Similarly, a number of different film-forming compounds known in the art can be used herein. Film-forming compounds suitable for use herein are compounds which are soluble in water and whose aqueous solutions dry to form a self-supporting film. Additionally, the film-forming compound must, of course, be compatible with

the selected gel-former and preferably should be miscible therewith to avoid phase separation. Further, the film-forming compounds should be non-toxic and non-antigenic. Moreover, the film-forming compound desirably should enhance the gel strength, sol-gel transition temperature, or gel setting time of the composition.

We currently prefer to use hydroxyethylcellulose, hydroxypropylmethylcellulose or polyvinyl alcohol as the film-forming ingredient. Low viscosity grade hydroxyethylcellulose, such as that sold by Hercules, Inc. UK under the trade mark "Natrosol 250L" and with a viscosity (5% aqueous solution at 25°C, Brookfield viscometer) in the range 100-180 centipoises, is especially advantageous since not only can it be incorporated in relatively high concentrations, for good film-forming properties, without unduly increasing the viscosity of the compositions at the time of application, but more particularly because it is highly compatible and miscible with Pluronic F127, our preferred gel-forming compound, and actually serves to enhance the gel strength of this gel-forming compound at gel setting temperatures. Thus, whereas, for instance, the viscosity of Pluronic F127 (10% w/w) in water is typically 0.2 poise, and the viscosity of Natrosol 250L (10% w/w) in water is typically 2.3 poises, that of a mixture of Pluronic F127 and Natrosol 250L (each at 10% w/w) in water is typically 9,500 poises, producing a very strong and rigid gel. (These viscosity measurements were all made at 25°C using a Brookfield viscometer.) These results are highly surprising since, as is taught in US-A-4474753, for instance, it has previously been considered that the ability to obtain a gel of desired rigidity at physiologically useful sol-gel transition temperatures using commercially available "Pluronic" polymers has been limited.

Again, mixtures of film-forming compounds can be used if desired, or for the purpose of obtaining specific properties.

The aqueous vehicle will normally consist of water alone, although in some instances it may also comprise small amounts e.g. up to 20% w/w, of a miscible, non-toxic and non-antigenic organic liquid e.g. ethanol or polyethylene glycol, for example in order to improve the conformability and plasticity of compositions containing relatively larger concentrations of the film-forming component.

As indicated above, other ingredients may optionally be included in the wound treatment compositions of this invention in order to modify their properties. For instance, we have found that incorporating a plasticizer enhances the elasticity of the set film and the adherency of the film to the wound surface. Suitable plasticizers include polyethylene glycol, glycerol, sorbitol, ethanolamine and calcium chloride. We currently, prefer to incorporate polyethylene glycol, more especially PEG 400 in amounts of from 1% to 10% by weight of the composition in those compositions which are formulated so as to be adapted for the treatment of superficial wounds. However, we prefer to omit a plasticizer from compositions formulated for the treatment of deep-seated wounds.

Another optional ingredient is a preservative, to protect the composition from microbial contamination during manufacture and storage and during the time it is on a patient. Benzyl alcohol in a concentration of about 0.5 to 2% by weight based on the weight of the composition, preferably about 1%, has been found to be a satisfactory preservative, but other suitable preservatives include methyl and propyl parabens, chlorbutanol, benzalkonium chloride, ascorbate, sodium

thiosulfate, sodium bisulfite, thimerosal and 2-phenoxyethanol. Benzyl alcohol has the effect of lowering the gelation temperature, and this effect therefore needs to be taken into account in determining the amounts of the other ingredients when benzyl alcohol is included.

In general, the pH of the present compositions can range from pH 3 to pH 9. Gelling temperature and strength may be affected to some extent by the pH of the composition, although we have found that a pH within the range of 5-7.5 generally has no significant effect on either gel strength or gel temperature, and we therefore prefer to operate within this range, since also it provides an inhibitory effect on bacterial cell growth. Most desirably, the pH of the present compositions is from 6.2 to 6.5. If necessary, the pH of the compositions can be adjusted to achieve a desired level using any pharmaceutically acceptable acid or base. Sodium hydroxide or ethanolamine, for instance, may be used to raise the pH, whilst hydrochloric acid is suitable for reducing pH.

The compositions of this invention may also, if desired, incorporate pharmaceutically active ingredients, for example antibacterial agents for the control of infection, chemotactic agents to induce the migration of normal fibroblasts and/or angiogenic agents to promote rapid re-epithelisation.

It is of course necessary that the wound dressing compositions of this invention should be sterile at the time of administration. We prefer to sterilize those compositions containing relatively smaller amounts of the gel-forming component by gamma irradiation, whereas those compositions containing relatively larger amounts of the gel-former are not successfully sterilized by this technique; for the latter compositions, heating

in an autoclave using a standard pharmacopoeial cycle is the preferred method. Whichever sterilization method is adopted, it is preferred to conduct the sterilization after filling the compositions into flexible sachets for dispensing. Containers other than sachets, eg aerosol spray containers or tube dispensers could, of course, also be used. The filled sachets or other containers can, if desired, be stored under refrigeration, but it appears that storage at ambient temperatures does not adversely affect the reversible gelation properties of the compositions, although if the product has been stored at a temperature above its sol-gel transition temperature it will then need to be cooled to below this temperature prior to administration.

The preferred wound treatment compositions of this invention have a number of advantages. In particular, the compositions possess a combination of both film- and gel-forming properties, which can be varied by appropriate selection of the components, and amounts thereof, as described above, so as to render them particularly suitable for different indications, e.g. treatment of superficial or deep-seated wounds. Moreover, they offer the practical advantage of forming a gelatinous-film in situ at the wound site, being easy both to apply and remove with the minimum of trauma to the patient. In the treatment of burns, the cooling effect which occurs <u>in situ</u> as the composition gels can be soothing to the patient. The gelatinous-film which forms on setting itself has a number of important advantages as a wound dressing, as hereinbefore indicated.

The invention is illustrated by the Examples which follow:

A wound dressing of the following composition was prepared.

Example 1

Pluronic F127	2.5%	10g
Hydroxyethylcellulose*	10.0%	40g
Benzyl alcohol	1.0%	16g
PEG 400	4.0%	4g
Purified water to	100.0%	330g

* "Natrosol 250L"

Hydroxyethylcellulose (40g) was slowly and carefully added to purified water (330g) at room temperature with continuous agitation to produce a clear colourless solution. PEG 400 (16g) and benzyl alcohol (4g) were added and thoroughly mixed with the hydroxyethylcellulose solution, and this was transferred to an ice-bath and cooled to 3-4°C. Pluronic F127 (10g) was slowly added to the cold solution with gentle mixing, and allowed to hydrate and dispersed overnight at 3-4°C to produce a clear colourless solution, the film former product.

Aliquots of the resulting solution were filled in to 3 layer laminate pouches (polyester/foil/-polyethylene), heat sealed and terminally sterilized by γ-irradiation (2.5 m Rads).

The pH of the final solution was measured at 4.9 and adjusted to pH 6.4 using 1N NaOH.

Viscosity** at 3-4°C	86.1 poise
Viscosity** at 25°C	134.4 poise
Sol-Gel transition temperature	22°-25°C

** measured using a Brookfield Model LVF viscometer

This product does not gel strongly, but forms a tough, flexible, transparent film which dries on the skin in approximately 15 minutes

Example 2

A further wound dressing was prepared, having the following composition:

Pluronic F127	10%	40g
Hydroxyethylcellulose*	10%	40g
Benzyl alcohol	1%	4g
Purified water to	100%	316g

* "Natrosol 250L"

The composition was prepared by the method described in Example 1.

Final pH of formulation; unadjusted	5.24
Viscosity** at 3°-4°C	165 poise
Viscosity** at 25°C	9540 poise
Sol-Gel Transition Temperature	16°-18°C
Gel-setting time	4-5 minutes

** measured using Brookfield LVF viscometer

When the benzyl alcohol was omitted, and the concentration of Pluronic F127 was increased to 11% (i.e. 44 g), the properties of the resulting wound dressing were as follows:

Final pH of formulation; unadjusted	6.17
Viscosity** at 3°-4°C	141.8 poise
Viscosity** at 25°C	12,360 poise
Sol-Gel Transition temperature	15°-18°C
Gel setting time	4-5 minutes

** measured using Brookfield LVF viscometer

Example 3

This example illustrates a wound dressing in accordance with this invention which includes an antibacterial agent.

Following the method of Example 1, a wound dressing of the following composition was prepared.

Pluronic F127		10%	40g
Hydroxyethylcellulose*		10%	40g
Chlorhexidine acetate		0.5%	2g
Purified water	to	100%	318g

* Natrosol 250L

The properties of this wound dressing were as follows:

Final pH of formulation; unadjusted	6.1
Viscosity** at 3°-4°C	183 poise
Viscosity** at 25°C	9300 poise
Sol-gel transition temperature	18°-20°C

** measured using Brookfield LVF viscometer

CLAIMS:

1. A wound dressing composition comprising an aqueous vehicle containing (a) from 1% to 30% by weight of one or more compounds having reversible thermosetting gel properties, and (b) from 5% to 20% by weight of one or more compounds, compatible with component (a) having film-forming properties, said percentages being based on the total weight of components (a) and (b) and aqueous vehicle in the composition, and the composition having a sol-gel transition temperature within the range 10° to 30°C, a viscosity of not greater than 250 poise, as determined by a Brookfield viscometer, at a temperature immediately below its sol-gel transition temperature whereby the mixture is pourable onto a wound to be treated when below said transition temperature, and in contact with the skin setting to form a non-flowable gelatinous wound dressing.

2. A wound dressing composition according to Claim 1, having a sol-gel transition temperature of from 10° to 25°C.

3. A wound dressing composition according to Claim 1 or Claim 2, having a viscosity of 50 to 250 poise, as determined by a Brookfield viscometer, immediately below its sol-gel transition temperature.

4. A wound dressing composition according to any preceding claim, wherein the gel-forming component exhibits reversible thermosetting gel properties at a temperature within the range 10°-45°C.

5. A wound dressing composition according to any preceding claim, comprising 1% to 5% by weight of the gel-forming component (a) and from 5% to 20% by weight of the film-forming component (b), said percentages being

based on the total weight of components (a) and (b) and aqueous vehicle in the composition, the composition setting in contact with the skin to form a coherent film thereon.

6. A wound dressing composition according to Claim 5 and including also a plasticizer.

7. A wound dressing composition according to Claim 6, comprising from 2% to 3% by weight of the gel-forming component (a), from 8% to 12% by weight of the film-forming component (b) and from 1% to 10% by weight of the plasticizer, said percentages being based on the total weight of the composition.

8. A wound dressing composition according to Claim 6 or Claim 7, wherein the plasticizer is polyethylene glycol.

9. A wound dressing composition according to any one of Claims 1-4, comprising from 5% to 30% by weight of the gel-forming component (a) and from 5% to 15% by weight of the film-forming component (b), said percentages being based on the total weight of components (a) and (b) and aqueous vehicle in the composition, the composition setting in contact with the skin to form a rigid gel.

10. A wound dressing composition according to Claim 9, comprising from 7% to 20% by weight of the gel-forming component (a) and from 7% to 12% by weight of the film-forming component (b), said percentages being based on the total weight of the composition.

11. A wound dressing composition according to any preceding claim and including also a preservative.

12. A wound dressing composition according to Claim 11, comprising from 0.5 to 2% by weight based on the total weight of the composition of benzyl alcohol.

13. A wound dressing composition according to any preceding claim, having a pH in the range 5 to 7.5.

14. A wound dressing composition according to Claim 13, having a pH in the range 6.2 to 6.5.

15. A wound dressing composition according to any preceding claim, and including also one or more biologically and/or pharmaceutically active components.

16. A sterile wound dressing composition according to any preceding claim.

17. A sterile wound dressing composition according to Claim 16 in a container for dispersing onto a wound site.

Published 1990 at The Patent Office, State House, 66-71 High Holborn, London, WC1R 4TP. Further copies may be obtained from The Patent Office, Sales Branch, St Mary Cray, Orpington, Kent BR5 3RD. Printed by Multiplex techniques ltd, St Mary Cray, Kent, Con. 1/87